ANTIFUNGAL AND ANTIPARASITIC COMPOUNDS

This application claims benefit of Provisional No. 60/097,672 filed May 24, 1998.

FIELD OF THE INVENTION

Compounds are described which represent novel, efficacious, and less toxic alternatives to current antiparasitic/antifungal treatments. Compounds having action via the biochemical mechanism of inhibition of lipid synthesis and/or metabolism and/or excretion, either by direct or indirect inhibition, will have either singly or in combination antiparasite/antifungal activity. Such compounds, in most cases, are not chemically related by structure or chemical class to each other. The compounds are identified as antiparasitics and/or antifungals based on mechanism of physiologic action. Data supporting "novel use" as antiparasite/antifungal compounds are given. Many compounds herein described are FDA-approved and marketed for human use for nonparasitic/nonfungal indications. Thus, the human pharmacokinetics for oral absorption, elimination rates/mechanisms, and dose-related toxicity are known.

INTRODUCTION

Status of Leishmaniasis, trypanosomiasis, and trichomoniasis

Current drugs most frequently used to treat leishmaniasis all require parenteral administration, date back 40→50 years, and all have such severe side-effects that treatment only in a hospital setting is recommended (Bryceson, 1968, *East African Med J* 45, 110–117; Bryceson, A., 1987, *The Leishmaniases in Biology and Medicine, Vol II Clinical Aspects and Control,* Academic Press, New York, pp. 847–907). No antileishmanial is Food and Drug Administration (FDA) approved and there is no chemoprophylaxis for any leishmanial disease. Topical treatment for leishmanial disease is not effective even for cutaneous disease forms because leishmaniasis is a systemic disease (Neva, et al., 1997, *Trans R Soc Trop Med Hyg* 91, 473–475). There is no general vaccine for leishmaniases, although a live vaccine is used in the Middle East for certain Leishmania (Leishmania) tropica/Leishmania (Leishmania) major to prevent facial scarring. Drug resistance is so severe in certain endemic regions that thousands are dying in India of untreatable, multidrug resistant visceral leishmaniasis; and in Northern Africa as a result of malnutrition exacerbated disease (Cerf, et al., 1987, *J Inf Dis* 156, 1030–1033; de Beer, et al., 1991, *Am J Trop Med Hyg* 44, 283–289; Sundar, 1997, *Acta Parasitol Turicica* 21, suppl 1, 128).

Immunodeficiency, either as the result of leishmanial tubercular- or HIV coinfections, poses serious therapeutic difficulties as leishmanial coinfection is reported to potentiate the pathology of both these bacterial and viral infections (Alvar, et al., 1997, *Clin Microbiol Rev* 10, 298–319; Bernier R, et al., 1995, *J Virol* 69, 7282–7285; Bryceson, 1987, supra; Faraut-Gamarelli, et. al., 1997, *Antimicrob Agents Chemother* 41, 827–830). Global travel and commerce result in patients having complex disease exposure history, and transportation of leishmanial parasites far from their anticipated endemic regions making both diagnosis and patient management difficult (Albrecht, et al., 1996, *Arch Pathol Lab Med* 120, 189–198). Leishmaniases have an annual incidence of 2–3 million new cases per year with 12 million infected and 350 million at risk in 88 countries worldwide (Croft, 1988, *Trends Pharmacol Sci* 9, 376–381; World Report on Tropical Diseases, 1990). The need for a orally administered antileishmanial of low toxicity is critical.

Two major groups of diseases caused by flagellate protozoa are African sleeping sickness (*Trypanosoma brucei* spp.) and trichomoniasis (Trichomonas/Tritrichomonas) exhibited as *trichomoniasis vaginalis* and trichomoniasis foetus.

African trypanosomiasis affects both domestic and wild animals as well as humans in mainly rural settings (Kuzoe, 1993, *Acta Tropica* 54, 153–162; World Health Organization (WHO), 1995, *Tropical Disease Research,* Twelfth Programme Report, Geneva Switzerland) while trichomoniasis is a cosmopolitan disease in men as well as women, and a threat to cattle breeding in most agricultural areas of the world (Hammill, 1989, *Obstet Gynecol Clin North Am* 16, 531–540; Levine, 1985, *Veterinary Protozoology.* Iowa State Univ. Press, Ames, pp 59–79). Treatment of the organisms causing these diseases presents problems, in part, due to the toxicity of existing agents, and the development of resistance to existing drugs (Kuzoe, 1993, supra; Lossick, 1989, *Trichomonads Parasite in Humans.* Springer-Verlag, New York, pp 324–341).

African trypanosomiasis is endemic in over 10 million square kilometers of sub-Saharan Africa, affecting humans and all domesticated livestock (WHO, 1995, supra). There are an estimated 25,000 new cases of human disease yearly and an animal incidence of 250–300,000 cases but these estimates are low, based on recent civil unrest and lapses in local tsetse fly control and medical surveillance (WHO, 1995, supra). The primary drugs for human and veterinary trypanosomiasis have been in use for >50 years. Resistance is spreading, especially to the only available agent for late stage central nervous system (CNS) human disease, melarsoprol (van Nieuwenhove, 1992, *Ann Soc Belg Med Trop* 72, 39–51; Kuzoe, 1993, supra). Melarsoprol is also toxic, with a 3–5% incidence of cerebral episodes reported (Pepin and Milord 1994, *Adv Parasitol* 33, 2–47; Wery, 1994, *Int J Antimicrob Agents* 4, 227–238). Veterinary trypanocides include diminazene (Berenil®) and isometamidium (Samorin®) which are used prophylactically for control of disease in cattle herds (WHO, 1995, supra; Kaminsky et al., 1993, Acta Tropica 54, 19–30). Resistance to both agents has been documented in field studies (Kuzoe, 1993, supra; Schoenfeld et al., 1987, *Trop Med Parasitol* 38, 117–180; Williamson, 1970, *The African Typanosomiases.* Allen & Unwin, London, pp 125–224). For these reasons, there is an urgent need to develop new trypanocides.

Trichomonas vaginalis is one of the most prevalent sexually transmitted pathogen of the human urogenital tract. It infects the vaginal epithelium, causing severe irritation and the development of a discharge. In addition to social distress caused by the disease, recent evidence suggests a high incidence rate between cervical cancer and trichomoniasis (Gram et al., 1992, *Cancer Causes and Control* 3, 231–236). The disease is widespread, with about 3 million cases in women annually in the United States alone (Hammill, 1989, supra). Chemotherapy for human trichomoniasis relies on a group of 5'-nitroimidazoles, with metronidazole (Flagyl®) being the most utilized. In the United States, metronidazole is the only available agent, although other derivatives are used in Europe and other areas. Since metronidazole has been in continuous use since 1955, there has been increasing reports of metronidazole-resistant vaginitis (Meingassner & Thurner, 1979, *Antimicrob Agents Chemother* 15, 254–258; Wong et al., 1990, *Australia-New Zealand J Obstet Gynecol*